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Knee cartilage defects: association with early radiographic osteoarthritis, decreased cartilage volume, increased joint surface area and type II collagen breakdown[1]

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Summary

Objective: To generate hypotheses regarding the associations between knee cartilage defects and knee radiographic osteoarthritis (ROA), cartilage volume, bone size and type II collagen breakdown in adults.

Methods: A cross-sectional convenience sample of 372 male and female subjects (mean age 45 years, range 26–61) was studied. Knee cartilage defect score (0–4) and prevalence (a defect score of ≥ 2), cartilage volume, and bone surface area were determined using T1-weighted fat saturation MRI. Urinary levels of C-terminal crosslinking telopeptide of type II collagen (U-CTX-II) were measured by enzyme-linked immunosorbent assay. Height, weight and ROA were measured by standard protocols.

Results: In multivariate analysis, the severity and prevalence of knee cartilage defects were significantly and independently associated with tibiofemoral osteophytes (regression coefficient (β): $+0.86$ to $+1.31$/unit, odds ratio (OR): 2.97–3.68/unit, all $P < 0.05$ with the exception of OR in lateral tibiofemoral compartment) and tibial bone area (β: $+0.11$ to $+0.25/cm^2$; OR: 1.33–1.58/cm^2, all $P < 0.01$). Knee cartilage defects were inconsistently associated with joint space narrowing after adjustment for osteophytes but consistently with knee cartilage volume (β: -0.27 to -0.70/ml; OR: 0.16–0.56/ml, all $P < 0.01$ except for OR at lateral tibial cartilage site $P = 0.06$). Lastly, knee cartilage defect severity was significantly associated with U-CTX-II (Partial $r = +0.18$, $P < 0.001$ for total cartilage defect score).

Conclusion: Osteophytes and increasing knee bone size may be causally related to knee cartilage defects. Furthermore, knee cartilage defects may result in increased cartilage breakdown leading to decreased cartilage volume and joint space narrowing suggesting an important role for knee cartilage defects in early knee OA.

Key words: Knee, Cartilage defects, Osteoarthritis, Volume, Bone area, Type II collagen.

Introduction

Osteoarthritis (OA) frequently affects the knee and is characterized by cartilage fissuring and erosion, osteophytes, subchondral sclerosis and cysts in later stages[1]. Knee cartilage defects are commonly found by arthroscopy in symptomatic subjects[2] where they are thought to be largely traumatic[3] but little is known about their causes or natural history. They may increase OA risk but there are limited data to support this. Preliminary studies have reported that knee cartilage defects are associated with Kellgren–Lawrence score in patients with advanced OA[4] and osteophytes in subjects with chronic knee pain[5]. The association between knee cartilage defects and early knee OA is unclear.

Measurement of joint space narrowing on weight-bearing plain radiographs represents a simple technique to assess the severity of chondropathy; however, it is indirect and mild, moderate and deep cartilage defects of the knee are likely to remain undetected on radiographs[6,7]. Magnetic resonance imaging (MRI) can visualize joint structure directly and non-invasively, and is recognized as a valid, accurate and reproducible tool to measure articular cartilage defects[8–10], knee cartilage volume and bone surface area[11–15]. Knee cartilage volume[16–19], tibial bone area[19] and urinary levels of C-terminal crosslinking telopeptide of type II collagen (U-CTX-II) as a marker of cartilage breakdown[20] have been reported to be associated with knee radiographic OA (ROA), but the associations between knee cartilage defects and cartilage volume, tibial bone area and type II collagen breakdown are unclear. The aim of this study, therefore, was to generate hypotheses regarding the association of knee cartilage defects with early ROA, cartilage volume, bone size and type II collagen breakdown in a convenience sample of adult males and females.

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Materials and methods

SUBJECTS

The study was carried out in Southern Tasmania primarily in the capital city of Hobart from June 2000 until December 2001. It was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee and all subjects provided informed written consent.

A convenience sample was utilized for this study. Subjects were selected from two sources with different family histories of OA. Half of the subjects were the adult children of subjects who had a knee replacement performed for primary knee OA at any Hobart hospital in the years 1996–2000. This diagnosis was confirmed by reference to the medical records of the orthopedic surgeon and the original radiograph where possible. The other half were randomly selected controls. These were selected by computer generated random numbers from the most recent version of the electoral roll (2000). Subjects from either group were excluded on the basis of contraindication to magnetic resonance imaging (MRI) (including metal sutures, presence of shrapnel, iron filing in eye and claustrophobia). No women were on hormone replacement therapy at the time of the study.

ANTHROPOMETRICS

Weight was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707) which were calibrated using a known weight at the beginning of each clinic. Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. Body mass index (BMI) (kg/m^2) was calculated. Knee pain was determined by self-administered questionnaire if subjects answered yes to the following question: Have you had knee pain for more than 24 h in the last 12 months or daily pain on greater than 30 days in the last year?

X RAY

A standing AP semiflexed view of the right knee was performed in all subjects. Radiographs were then assessed utilizing the Altman atlas[21]. Each of the following was assessed: medial joint space narrowing (0–3), lateral joint space narrowing (0–3), medial osteophytes (femoral and tibial combined) (0–3) and lateral osteophytes (femoral and tibial combined) (0–3). Each score was arrived at by consensus with two readers (GJ, FS) simultaneously assessing the radiograph with immediate reference to the atlas. Reproducibility was assessed and yielded an intra-class correlation coefficient (ICC) of 0.99 for osteophytes and 0.98 for joint space narrowing[14,19].

KNEE CARTILAGE VOLUME MEASUREMENT

An MRI scan of the right knee was performed. Knee cartilage volume was determined by means of image processing on an independent work station using the software program Osiris as previously described[11–15]. Knees were imaged in the sagittal plane on a 1.5-T whole body magnetic resonance unit (Picker) with use of a commercial transmit–receive extremity coil. The following image sequence was used: a T1-weighted fat saturation three-dimensional (3D) gradient recall acquisition in the steady state; flip angle 55°; repetition time 58 ms; echo time 12 ms; field of view 16 cm; 60 partitions; 512×512 matrix; acquisition time 11 min 56 s; one acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31×0.31 (512×512 pixels). The image data were transferred to the workstation. The volumes of individual cartilage plates (medial tibial, lateral tibial and patella) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section by section basis. These data were then resampled by means of bilinear and cubic interpolation (area of 312 and 312 μm and 1.5 mm thickness, continuous sections) for the final 3D rendering. The volume of the particular cartilage plate was then determined by summing all the pertinent voxels within the resultant binary volume. Femoral cartilage volume was not assessed as we have published that two tibial sites and the patella site correlate strongly with this site (16). Using this method we had high intra- and interobserver reproducibility. The coefficient of variation (CV) for cartilage volume measures was 2.1% for medial tibial, 2.2% for lateral tibial and 2.6% for patella[11].

CARTILAGE DEFECTS ASSESSMENT

The cartilage defects were graded on the above magnetic resonance (MR) images with a modification of a previous classification system[8–10] at medial tibial, medial femoral, lateral tibial, lateral femoral and patellar sites as follows (Fig. 1): grade 0, normal cartilage; grade 1, focal blistering and intracartilaginous low-signal intensity area with an intact surface and base; grade 2, irregularities on the surface or base and loss of thickness of less than 50%; grade 3, deep ulceration with loss of thickness of more than 50%; grade 4, full-thickness chondral wear with exposure of subchondral bone. We found that cartilage surface in some images was still regular but cartilage adjacent to subchondral bone became irregular, so we included these changes in the classification system. A cartilage defect also had to be present in at least two consecutive slices. The cartilage was considered to be normal if the band of intermediate signal intensity had a uniform thickness. The cartilage defects were re-graded 1 month later and the average scores of cartilage defects at medial tibiofemoral (0–8), lateral tibiofemoral (0–8), patellar (0–4) and whole compartments (0–20) were used in the study. A prevalent cartilage defect was defined as a cartilage defect score of ≥ 2 at any site within that compartment. Intraobserver reliability (expressed as ICC) was 0.90 for the medial tibiofemoral compartment, 0.89 for the lateral tibiofemoral compartment, 0.94 for the patellar compartment and 0.94 for the total score. Interobserver reliability was assessed in 50 MR images and yielded an ICC of 0.90 for the medial tibiofemoral compartment, 0.85 for the lateral tibiofemoral compartment, 0.93 for the patellar compartment and 0.93 for the total score.

KNEE BONE SIZE MEASUREMENT

Knee tibial plateau bone area and patellar bone volume were determined as previously described[11–15,19] with CVs in our hands of 2.2–2.6%[11].

U-CTX-II MEASUREMENT

Overnight urine samples were collected in plastic containers. After mixing the whole collection, aliquots of urine were

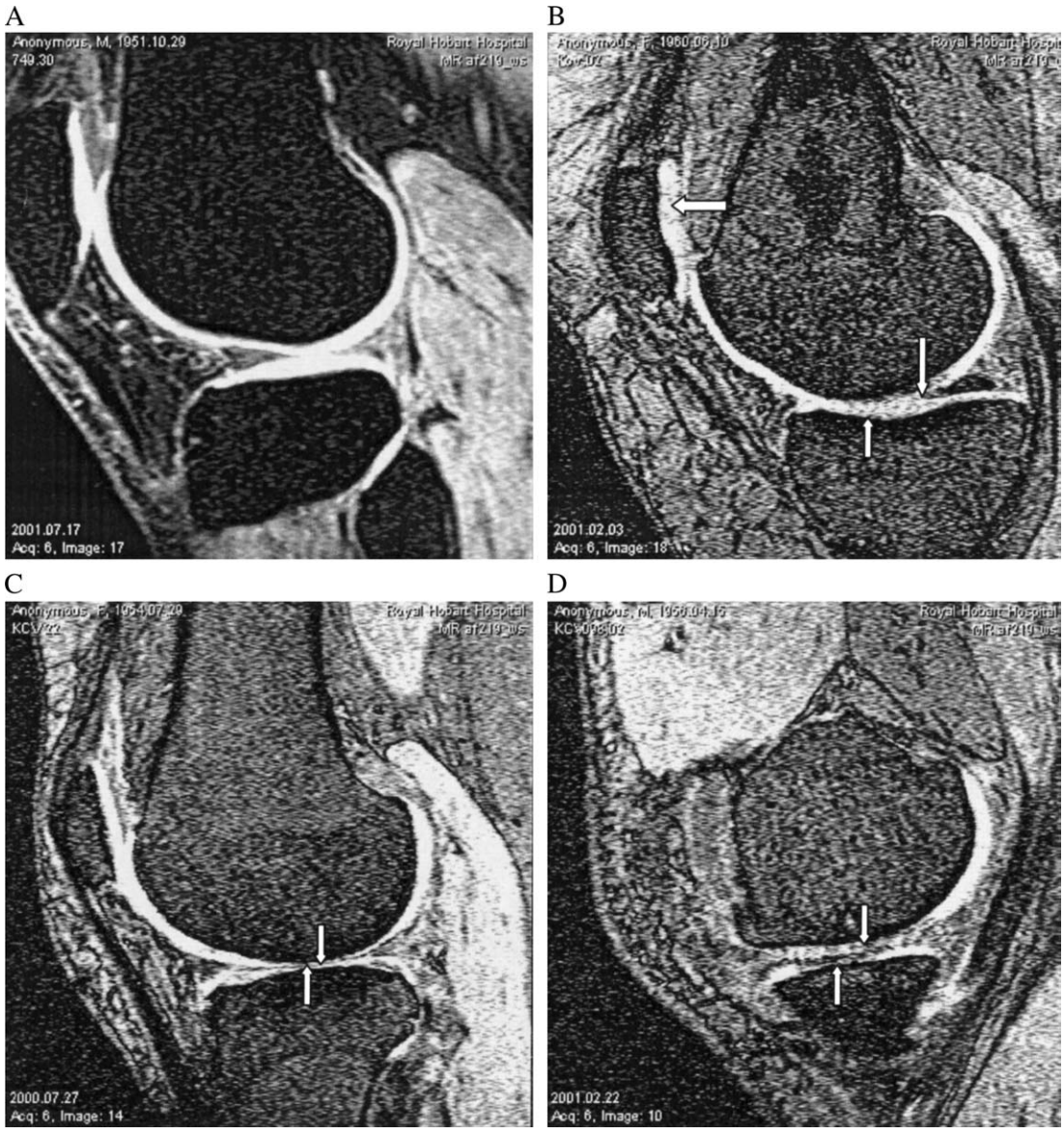

Fig. 1. Sagittal T1-weighted fat saturated 3D MRI images shows: (A) Normal lateral tibial, lateral femoral and patellar cartilage (grade 0). (B) Slight cartilage defects at lateral tibial and patellar site (grade 1) but moderate cartilage defects at lateral femoral site (grade 2). (C) Normal cartilage at patellar site (grade 0) but severe cartilage defects at lateral tibial and femoral sites (grade 3). (D) Severe cartilage defects at medial tibial (grade 4) and femoral (grade 3) sites.

transferred into plastic tubes and frozen at −70°C without any acidification. U-CTX-II was measured by an enzyme-linked immunosorbent assay based on a monoclonal antibody raised against the EKGPDP linear six amino acid epitope of the type II collagen C-telopeptide (Cartilaps, Nordic Biosciences, Herlev, Denmark). Intra- and inter-assay CVs are lower than 8% and 10%[20,22].

STATISTICS

t test or Mann–Whitney *U* test (where appropriate) were used to compare means. Linear regression analysis was used to examine the associations between knee cartilage defects, ROA, cartilage volume and bone size before and after adjustment for age, sex, BMI, family history, cartilage volume if bone size and bone size if cartilage volume. For cartilage defect scores in individual compartments the range and distribution were such that basic assumptions for applying linear regression did not hold. However, for the combined total score the assumptions did hold. For the sake of comparability we used linear regression to assess multivariable effects adjusting for other covariates for all score and total score variables. This seemed preferable to using an ordinal logistic regression model for a pooled score outcome and linear regression for total score. Logistic regression analysis was used to examine the associations between knee cartilage defect prevalence and other variables. U-CTX-II levels were not normally distributed ($P < 0.001$) and were log transformed for all analyses. Linear regression analysis was also used to examine the association between cartilage defect score and log transformed U-CTX-II. A *P* value less than 0.05 (two-tailed) or

a 95% confidence interval (CI) not including the null point was regarded as statistically significant. All statistical analyses were performed on SPSS version 10.0 for Windows (Chicago, IL).

Results

A total of 372 subjects (female 214, male 158) aged between 26 and 61 (mean 45 years) took part. Knee cartilage defects were common (44%) and varied in severity from grade 2–4 whereas ROA was uncommon (17%) and was predominantly grade 1. Demographic and study factors are presented in Table I. The prevalence of pain was 35%. In unadjusted analysis, subjects with and without knee cartilage defects were similar in terms of height, sex distribution, past knee injury history, tibial cartilage volume, patellar bone volume and U-CTX-II levels, but subjects with knee cartilage defects were older, and had higher weight, BMI, ROA prevalence, and tibial bone area but lower patellar cartilage volume.

Tables II and III document the associations between knee cartilage defect, joint space narrowing and cartilage volume. Knee cartilage defect scores and prevalence were significantly associated with joint space narrowing in tibiofemoral compartments both before and after adjustment for age, sex, BMI and family history. After further adjustment for osteophytes, these associations decreased by 35–60% for severity and became non-significant for prevalence in all compartments. Knee cartilage defect scores and prevalence were not associated with tibial cartilage volume, but were significantly associated with patellar cartilage volume in univariate analysis; however, knee cartilage defects in each compartment were significantly negatively associated with knee cartilage volume after adjustment for age, sex, BMI, family history and bone size. Similar results were obtained if subjects with ROA were excluded or men and women were analyzed separately (data not shown).

Tables IV and V document the associations between knee cartilage defects, osteophytes and bone size. Knee cartilage defect scores and prevalence were significantly associated with osteophytes in tibiofemoral compartments before and after adjustment for age, sex, BMI and family history. After further adjustment for joint space narrowing, these associations decreased by 7–12% for scores and remained significant for scores and prevalence except for prevalence in the lateral tibiofemoral compartment. Knee cartilage defect scores and prevalence were significantly associated with tibial bone area, but not patellar bone volume in univariate analysis. These associations remained significant for tibial bone area and became significant for patellar bone volume after adjustment for age, sex, BMI, family history and cartilage volume. Similar results were obtained if subjects with ROA were excluded or men and women were analyzed separately (data not shown). Knee cartilage defect severity in all compartments was significantly associated with U-CTX-II in total sample and women, but not in men (Fig. 2). These associations in total sample remained significant or of borderline significance after adjustment for age, sex, BMI and family history (Partial $r = +0.18$, $P = 0.001$ for total cartilage defect score; Partial $r = +0.08$, $P = 0.11$ for medial tibiofemoral cartilage defect score; Partial $r = +0.10$, $P = 0.055$ for lateral tibiofemoral cartilage defect score; Partial $r = +0.18$, $P = 0.001$ for patellar cartilage defect score). Prevalent knee cartilage defects were not significantly associated with U-CTX-II with the exception of prevalent patellar cartilage defects ($P = 0.048$).

Discussion

In this convenience sample of males and females, the severity and prevalence of knee cartilage defects were significantly associated with early knee ROA especially osteophytes and, to a lesser extent, joint space narrowing. They also were significantly positively associated with knee bone size and negatively associated with knee cartilage volume in all compartments. Furthermore, knee cartilage defect severity was associated with increased type II collagen breakdown.

Table I
Characteristics of participants

	No cartilage defects, $N = 210$	Any cartilage defects, $N = 162$	P Value
Age (years)	43.6 (7.1)	47.0 (6.1)	<0.01
Height (cm)	168.7 (8.0)	169.6 (9.0)	0.31
Weight (kg)	74.7 (13.8)	81.2 (16.6)	<0.01
BMI	26.2 (4.2)	28.2 (5.0)	<0.01
Male: female ratio	58% female	57% female	0.97*
Past knee injury (%)	18	21	0.49*
Any knee radiographic change (%)	10	26	<0.01*
Medial joint space narrowing (%)	9	20	<0.01*
Lateral joint space narrowing (%)	1	6	0.02*
Medial osteophytes (%)	2	13	<0.01*
Lateral osteophytes (%)	1	6	0.07*
Medial tibial cartilage volume (ml)	2.3 (0.6)	2.2 (0.6)	0.30
Lateral tibial cartilage volume (ml)	2.6 (0.6)	2.6 (0.7)	0.49
Patella cartilage volume (ml)	3.7 (0.9)	17.9 (2.9)	<0.01
Lateral tibial bone area (cm^2)	11.7 (1.8)	12.3 (2.2)	<0.01
Patella bone volume (ml)	13.7 (3.3)	13.9 (3.4)	0.72
ln U-CTX-II	4.8 (0.6)	4.9 (0.5)	0.52

Mean (SD) except for percentages.
U-CTX-II: Urinary C-terminal crosslinking telopeptide of type II collagen.
*Mann–Whitney U test, all others unpaired t test.

Table II
The associations between knee cartilage defect severity, joint space narrowing and cartilage volume

	Univariate β (95% CI)	Multivariate* β (95% CI)	Multivariate† β (95% CI)
MTF cartilage defects‡			
MTF JSN (per grade)	**+0.61 (+0.39, +0.82)**	**+0.55 (+0.34, +0.76)**	**+0.36 (+0.15, +0.57)**
MT cartilage volume (per ml)	−0.12 (−0.25, +0.01)	**−0.31 (−0.46, −0.16)**	**−0.45 (−0.61, −0.30)**
LTF cartilage defects‡			
LTF JSN (per grade)	**+0.87 (+0.50, +1.24)**	**+0.86 (+0.49, +1.22)**	+0.34 (−0.02, +0.70)
LT cartilage volume (per ml)	+0.08 (−0.03, +0.20)	−0.08 (−0.22, +0.06)	**−0.26 (−0.42, −0.11)**
Patellar cartilage defects‡			
PAT cartilage volume (per ml)	**−0.50 (−0.59, −0.41)**	**−0.60 (−0.71, −0.49)**	**−0.68 (−0.80, −0.57)**
Total cartilage defects‡			
TF JSN (per grade)	**+0.99 (+0.58, +1.41)**	**+0.73 (+0.33, +1.13)**	**+0.43 (+0.04, +0.83)**
Total cartilage volume (per ml)	**−0.18 (−0.28, −0.09)**	**−0.36 (−0.47, −0.24)**	**−0.55 (−0.67, −0.44)**

*Adjusted for age, gender, BMI and family history.
†Adjusted by previous factors and bone size if cartilage volume or osteophytes if joint space narrowing.
‡Dependent variables. MTF: medial tibiofemoral; LTF: lateral tibiofemoral; JSN: joint space narrowing; MT: medial tibial; LT: lateral tibial; PAT: patellar; TF: tibiofemoral.

Knee cartilage defects can occur through injury and trauma[3] and may predispose patients to radiographic change and clinical symptoms of knee OA. A recent study reported knee cartilage defects were frequently demonstrated on MRI in patients with advanced ROA but it is uncertain whether these cartilage defects lead to OA or more severe arthritis results in increased cartilage damage[4]. Furthermore, the association between knee cartilage defects and early ROA has not yet been reported. In the current sample, ROA was uncommon and was predominantly mild. However, knee cartilage defects were common and of varying severity, and were significantly associated with both early ROA and decreased cartilage volume. The causal direction of association is unclear from this cross-sectional study. Biologically, it would make sense to infer that osteophytes lead to cartilage defects through increased force transmission and that cartilage defects lead to joint space narrowing through increased cartilage loss. Our data on the association between cartilage defects and both cartilage volume and U-CTX-II are consistent with this explanation. Nevertheless, longitudinal studies will be required to more fully delineate causal directions.

Subchondral bone may have an important role to play in the initiation and progression of cartilage damage[23–25]. Previous studies have shown that knee cartilage defects on MRI were significantly associated with osteophytes on radiographs of the same joint[5], and that the presence of subchondral bone abnormalities and bone marrow edema on MRI at baseline predicted worsening of cartilage defects after 1 year[9]. We recently reported that there was a substantial 10–22% increase in lateral and medial tibial bone areas with grade 1 osteophytosis, but not with grade 1 joint space narrowing[19]. In the current study, the severity and prevalence of knee cartilage defects were significantly associated with osteophytes and bone size. These results were consistent in all compartments even though patellar bone size and tibial bone size were measured in different ways, supporting a role of subchondral bone expansion in the etiology of knee cartilage defects, particularly given that our grading scale included defects that were deep and thus adjacent to subchondral bone. The associations between cartilage defects and osteophytes or bone area were stronger than those between cartilage defects and joint space narrowing or cartilage volume, and the associations

Table III
The associations between knee cartilage defect prevalence, joint space narrowing and cartilage volume

	Univariate OR (95% CI)	Multivariate* OR (95% CI)	Multivariate† OR (95% CI)
Prevalent MTF defect‡			
MTF JSN (per grade)	**3.40 (1.76–6.57)**	**2.98 (1.44–6.18)**	2.20 (1.00–4.87)
MT cartilage volume (per ml)	0.66 (0.40–1.09)	**0.31 (0.16–0.61)**	**0.16 (0.07–0.36)**
Prevalent LTF defect‡			
LTF JSN (per grade)	**3.18 (1.12–9.05)**	**3.11 (1.00–9.64)**	2.40 (0.68–8.48)
LT cartilage volume (per ml)	1.18 (0.80–1.72)	0.81 (0.49–1.35)	0.59 (0.33–1.06)
Prevalent patellar defect‡			
PAT cartilage volume (per ml)	**0.33 (0.24–0.45)**	**0.27 (0.18–0.41)**	**0.20 (0.13–0.32)**
Prevalent any defect‡			
TF JSN (per grade)	**2.42 (1.44–4.07)**	**2.03 (1.16–3.53)**	**1.76 (1.00–3.09)**
Total cartilage volume (per ml)	**0.86 (0.77–0.95)**	**0.73 (0.62–0.86)**	**0.56 (0.45–0.68)**

*Adjusted for age, gender, BMI and family history.
†Adjusted by previous factors and bone size if cartilage volume or by osteophytes if joint space narrowing.
‡Dependent variables. MTF: medial tibiofemoral; LTF: lateral tibiofemoral; JSN: joint space narrowing; MT: medial tibial; LT: lateral tibial; PAT: patellar; TF: tibiofemoral.

Table IV
The associations between knee cartilage defect severity, osteophytes and bone size

	Univariate β (95%CI)	Multivariate* β (95% CI)	Multivariate† β (95% CI)
MTF cartilage defects‡			
MTF osteophytes (per grade)	**+1.11 (+0.85, +1.36)**	**+0.98 (+0.73, +1.23)**	**+0.86 (+0.60, +1.12)**
MT bone area (per cm^2)	**+0.06 (+0.03, +0.09)**	**+0.06 (+0.03, +0.10)**	**+0.11 (+0.07, +0.15)**
LTF cartilage defects‡			
LTF osteophytes (per grade)	**+1.39 (+1.10, +1.68)**	**+1.30 (+1.02, +1.59)**	**+1.20 (+0.90, +1.50)**
LT bone area (per cm^2)	**+0.13 (+0.09, +0.16)**	**+0.13 (+0.08, +0.18)**	**+0.17 (+0.11, +0.22)**
Patellar cartilage defects‡			
PAT bone volume (per ml)	−0.02 (−0.05, +0.01)	+0.02 (−0.03, +0.06)	**+0.08 (+0.05, +0.12)**
Total cartilage defects‡			
TF osteophytes (per grade)	**+1.65 (+1.24, +2.06)**	**+1.41 (+1.02, +1.81)**	**+1.31 (+0.91, +1.71)**
Total tibial bone area (per cm^2)	**+0.09 (+0.05, +0.13)**	**+0.13 (+0.07, +0.19)**	**+0.25 (+0.19, +0.31)**

*Adjusted for age, gender, BMI and family history.
†Adjusted for previous factors and joint space narrowing if osteophytes or cartilage volume if bone size.
‡Dependent variables. MTF: medial tibiofemoral; LTF: lateral tibiofemoral; MT: medial tibial; LT: lateral tibial; PAT: patellar; TF: tibiofemoral.

between knee cartilage defects and osteophytes changed little after adjustment for joint space narrowing, but the associations between knee cartilage defects and joint space narrowing decreased markedly after adjustment for osteophytes, suggesting subchondral bone changes with cartilage defects are primary, and subchondral bone change precedes cartilage damage in early knee OA.

Type II collagen is a major structural component of cartilage and is localized almost exclusively in this tissue. Hence, measurements of fragments derived from this protein such as U-CTX-II may potentially represent a specific index for cartilage breakdown. The U-CTX-II assay has showed high technical precision and ability to differentiate populations with an elevated joint metabolism from normal controls[22]. U-CTX-II levels are significantly raised[20,22] and associated with knee joint space width and area in established knee OA[20] and a recent report found the increased levels were significantly associated with the progression of chondropathy by arthroscopy after 1 year follow-up[26]. In the current sample with early knee ROA, we failed to find any association between U-CTX-II levels and joint space narrowing (data not shown); however, knee cartilage defect severity in all compartments measured by MRI was positively associated with U-CTX-II levels. These findings are in agreement with biochemical and histological studies indicating that type II collagen degradation is an early sign of cartilage damage[27,28]. The strength of association was modest but strongest for the total knee which is perhaps not surprising given that CTX-II comes from hyaline cartilage throughout the body and one knee only makes a small contribution to total hyaline cartilage. The association was significant in women but not in men. The reason for this is unclear but may suggest that women have greater susceptibility to cartilage defects, or may reflect a greater contribution to U-CTX-II from sites outside the knee in males due to their larger body size.

This study has a number of limitations. Firstly, the study was primarily designed to look at genetic mechanisms of knee OA and utilized a matched design. The matching was broken for the current study but adjustment for family history did not alter the results. Indeed, while there was a reduction in power, the results otherwise did not differ if examined in offspring and controls separately. While the sample is a convenience sample, Miettinen[29] states that for these associations to be generalizable to other populations three key criteria need to be met regarding selection, sample

Table V
The associations between knee cartilage defect prevalence, osteophytes and bone size

	Univariate OR (95% CI)	Multivariate* OR 95% CI)	Multivariate† OR 95% CI)
Prevalent MTF defect‡			
MTF osteophytes (per grade)	**6.78 (2.85–16.09)**	**4.65 (1.88–11.49)**	**3.68 (1.45–9.33)**
MT bone area (per cm^2)	**1.22 (1.10–1.35)**	**1.29 (1.10–1.51)**	**1.58(1.30–1.91)**
Prevalent LTF defect‡			
LTF osteophytes (per grade)	**3.77 (1.28–11.07)**	**3.18 (1.04–9.71)**	2.75 (0.81–9.34)
LT bone area (per cm^2)	**1.26 (1.11–1.44)**	**1.24 (1.03–1.50)**	**1.33 (1.09–1.63)**
Prevalent patellar defect‡			
PAT bone volume (per ml)	0.98 (0.91–1.05)	1.10 (0.99–1.22)	**1.28 (1.14–1.45)**
Prevalent any defect‡			
TF osteophytes (per grade)	**4.23 (1.70–10.48)**	**3.45 (1.35–8.82)**	**2.97 (1.16–7.61)**
Total tibial bone area (per cm^2)	**1.07 (1.02–1.13)**	**1.15 (1.06–1.25)**	**1.33 (1.20–1.48)**

*Adjusted for age, gender, BMI and family history.
†Adjusted for previous factors and joint space narrowing if osteophytes or cartilage volume if bone size.
‡Dependent variables. MTF: medial tibiofemoral; LTF: lateral tibiofemoral; MT: medial tibial; LT: lateral tibial; PAT: patellar; TF: tibiofemoral.

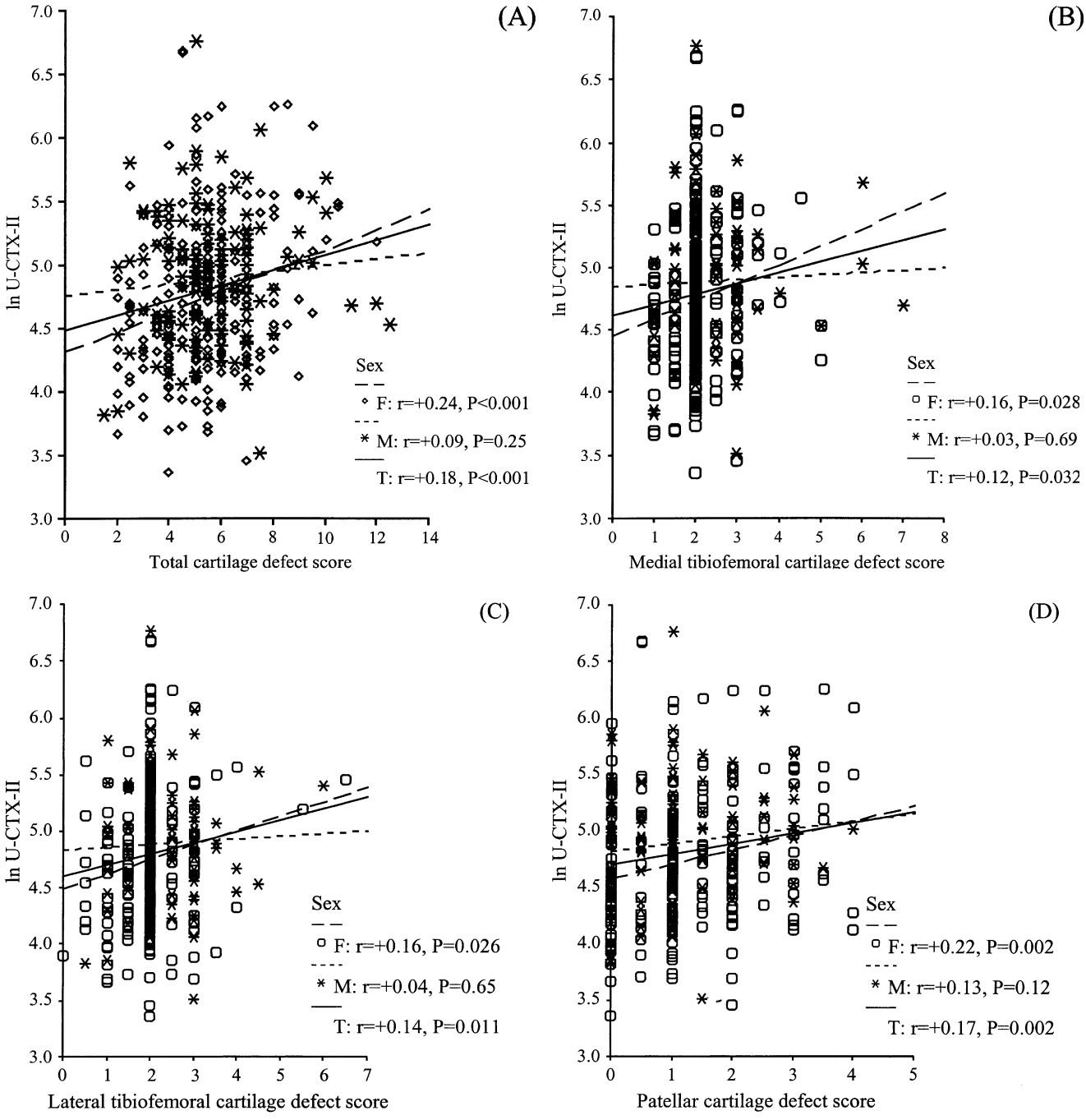

Fig. 2. Correlation between knee cartilage defects and U-CTX-II. There were significant positive associations between CTX-II and knee cartilage defect severity in all compartments in total sample and women, but not men. T: total sample; F: females; M: males.

size and adequate distribution of study factors all of which are met by this study. Secondly, measurement error may influence results. However, knee cartilage defects scoring, cartilage volume, bone size, ROA and CTX-II measurement[11–15,20,22] were all highly reproducible suggesting that this is unlikely.

In conclusion, this cross-sectional study suggests osteophytes and increasing knee bone size may be causally related to knee cartilage defects. Furthermore, knee cartilage defects may result in increased cartilage breakdown leading to decreased cartilage volume and joint space narrowing suggesting an important role for knee cartilage defects in early knee OA.

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